Clinical Pharmacology Advisory Committee Meeting
Topic 4: Transporter-Mediated Drug-Drug Interactions
Atlanta, GA, March 17, 2010

Transporter-Mediated Drug-Drug Interactions (DDIs)

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Drug Transporters: Contribute to variability in drug concentration and response

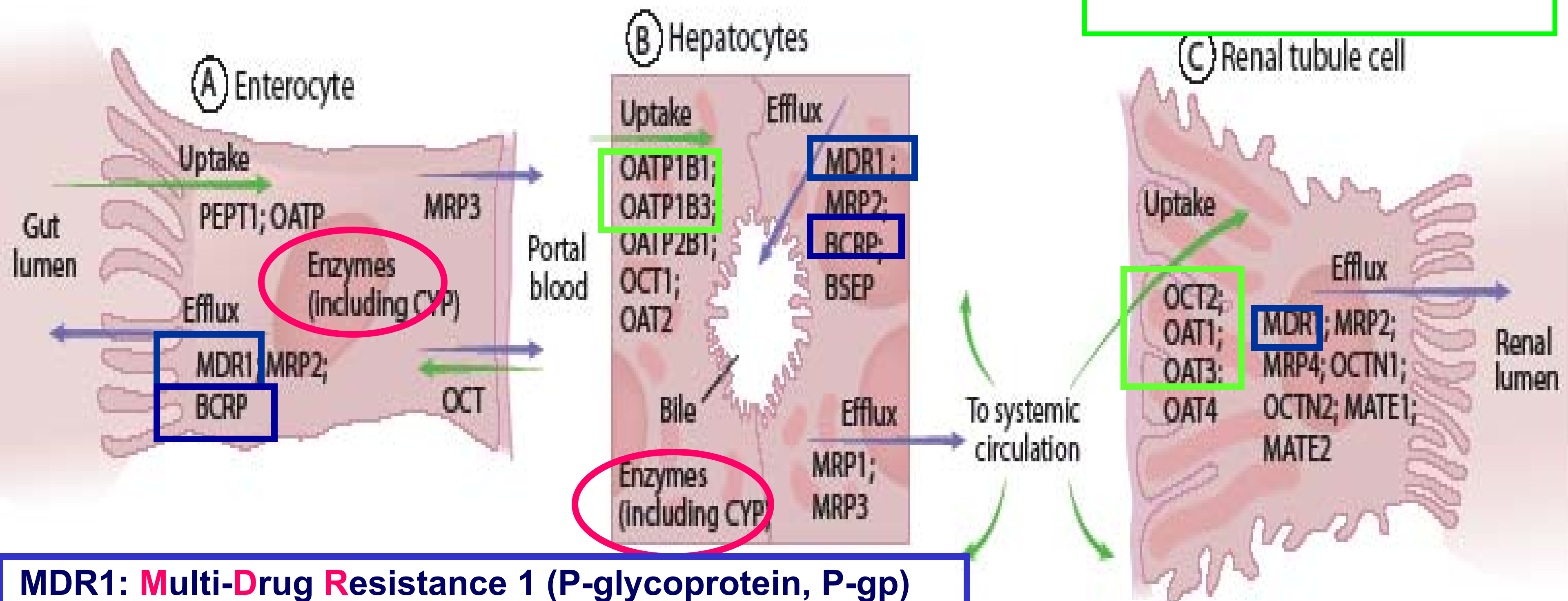
- Pharmacokinetic determinant
  - **A**bs tion
  - **D**istrib
  - **M**
  - **E**
- P inant
  - Deliv site action
  - Contr of tissue concentrations
  - Discovery Targets

May cause unexpected toxicities or drug-drug interactions

Selected efflux & uptake transporters in the gut wall (A), liver (B), and kidney (C)

OCT2: Organic

OATP: Organic Anion Transporting Polypeptide



MDR1: Multi-Drug Resistance 1 (P-glycoprotein, P-gp)
BCRP: Breast Cancer Resistance Protein
In liver, intestine, kidney, brain

Huang, Lesko, and Temple, "Adverse Drug Reactions and Pharmacokinetic Drug Interactions", Chapter 21, Adverse Drug Reactions and Drug Interactions in Part 4, FUNDAMENTAL PRINCIPLES: Clinical Pharmacology, "Pharmacology and Therapeutics: Principles to Practice," Ed. Waldman & Terzic, Elsevier, 2009

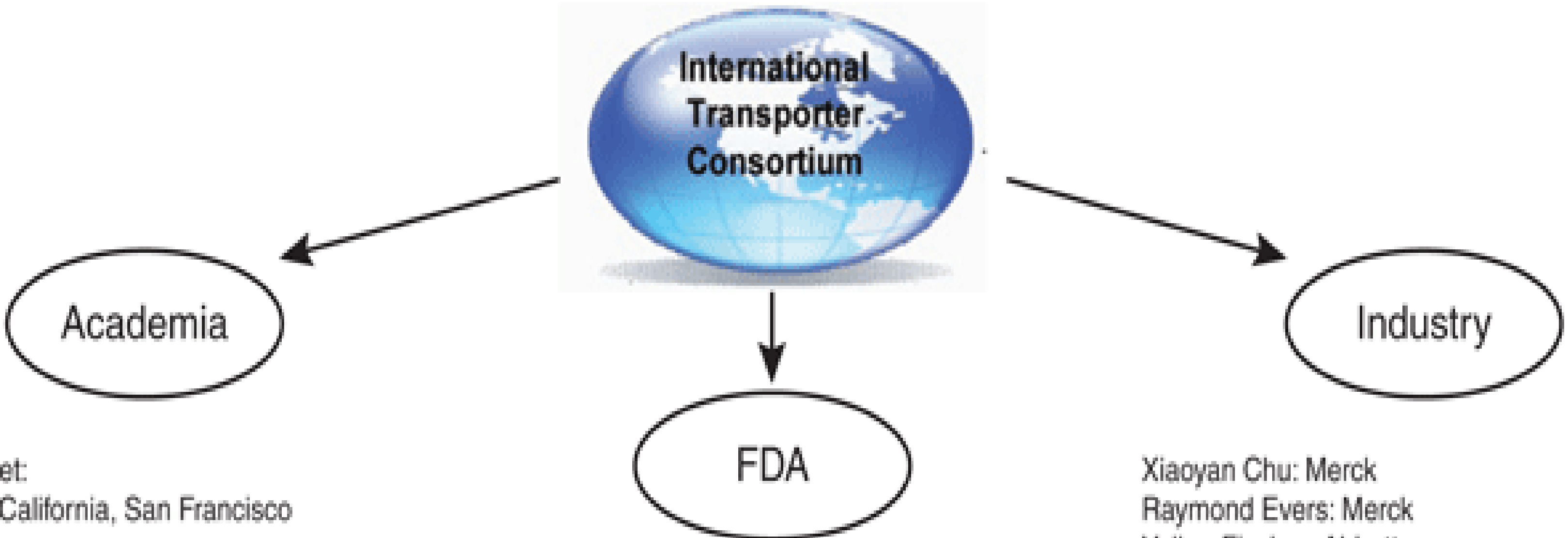
Examples of Transporter-Mediated Drug Interactions

Interacting Drug	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Quinidine	Digoxin	Digoxin Exposure 1.7-fold ↑	P-glycoprotein (P-gp, MDR1) Inhibition
Rifampin	Digoxin	Digoxin Exposure 30% ↓	P-gp Induction
Dronedarone	Digoxin	Digoxin Exposure 2.6-fold ↑	P-gp Inhibition
Probenecid	Cephradine	Cephradine Exposure 3.6-fold ↑	Organic Anion Transporter (OAT) Inhibition
Cimetidine	Metformin	Metformin Exposure 1.4-fold ↑	Organic Cation Transporter (OCT) Inhibition
Cyclosporine	Rosuvastatin	Rosuvastatin Exposure 7-fold ↑	Organic Anion Transporting Polypeptide (OATP) Inhibition & Breast Cancer Resistance Protein (BCRP) Inhibition
Lopinavir/ Ritonavir	Rosuvastatin	Rosuvastatin Exposure 2-fold ↑	OATP Inhibition

Which transporters are clinically important and should be considered for evaluation during drug development?

- For new molecular entity (NME) as a substrate
- For new molecular entity (NME) as an inhibitor

International Transporter Consortium



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<Huang, SM, Zhang L, Giacomini KM, Clin Pharmacol Ther January 2010>

Transporter White Paper

1. Overview of Transporters

Overview, P-gp, BCRP, OAT/OCT, OATP (7 transporters)

2. Methods for Studying Transporters

Cell/membrane models, intact organ/in vivo models; modeling/imaging tools, enzyme/transporter interplay

3. Drug Development Issues

Overview/example cases; decision trees

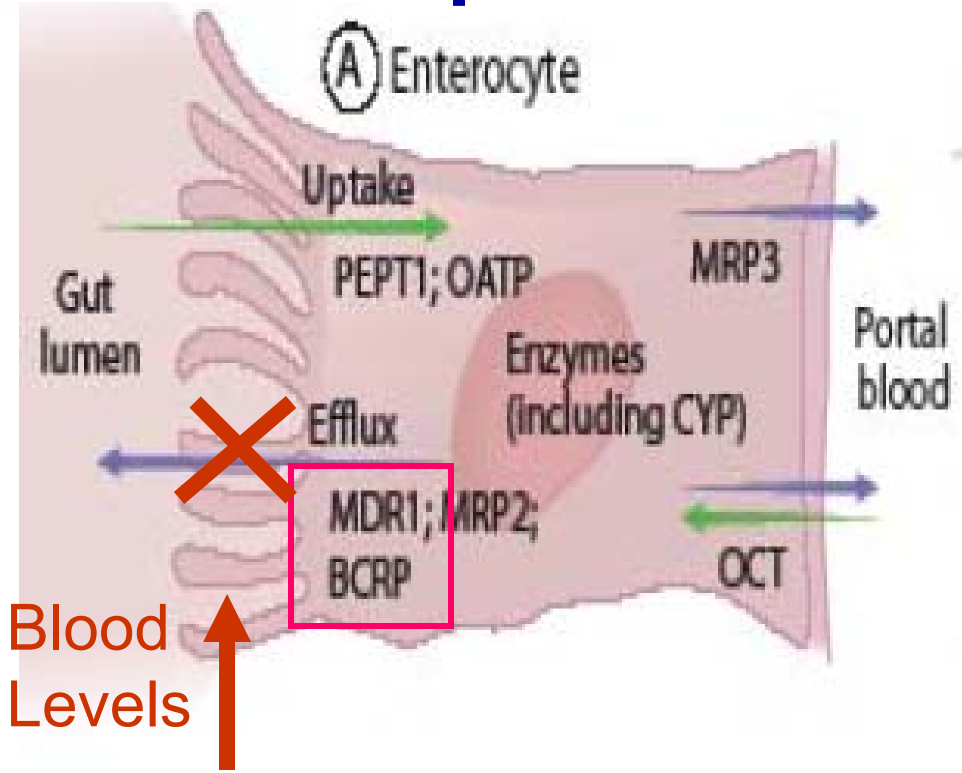
Giacomini, Huang, Tweedie et al, Nature Reviews Drug Discovery 2010, 9, 215-236.

Transporters in Drug Absorption
Important Intestine Transporters

Efflux

(to intestinal lumen):

- P-glycoprotein (P-gp, MDR1, ABCB1)
- Breast Cancer Resistance Protein (BCRP, ABCG2)



Inhibitor	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Quinidine	Digoxin	Digoxin Exposure ↑	1.7-fold ↑
GF120918	Topotecan	Topotecan Exposure ↑	2.4-fold ↑

Transporters in Drug Distribution, Uptake and Excretion—Important Liver Transporters

Uptake

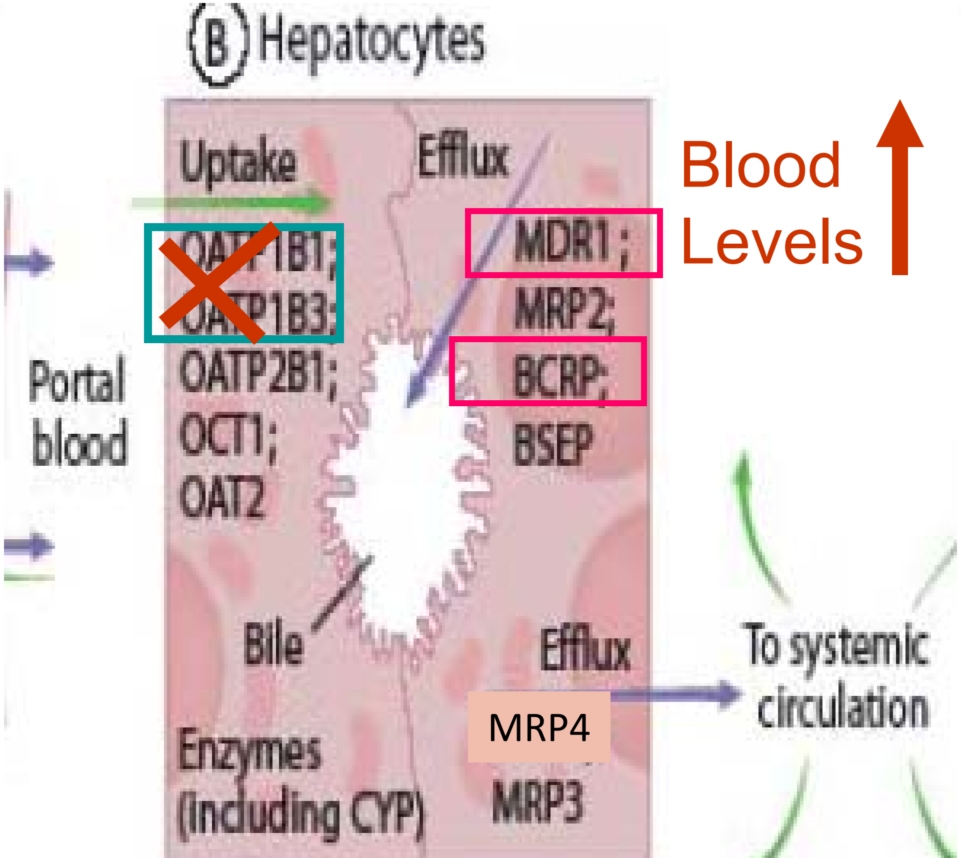
(from blood to hepatocytes):

- OATP1B1
- OATP1B3

Efflux

(excretion to bile):

- P-gp
- BCRP



Inhibitor	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Cyclosporine	Rosuvastatin	Rosuvastatin Exposure ↑	7-fold ↑
Lopinavir/ Ritonavir	Rosuvastatin	Rosuvastatin Exposure ↑	2-fold ↑

Transporters in Drug Distribution, Uptake and Excretion—Important Kidney Transporters

Uptake

(from blood to kidney):

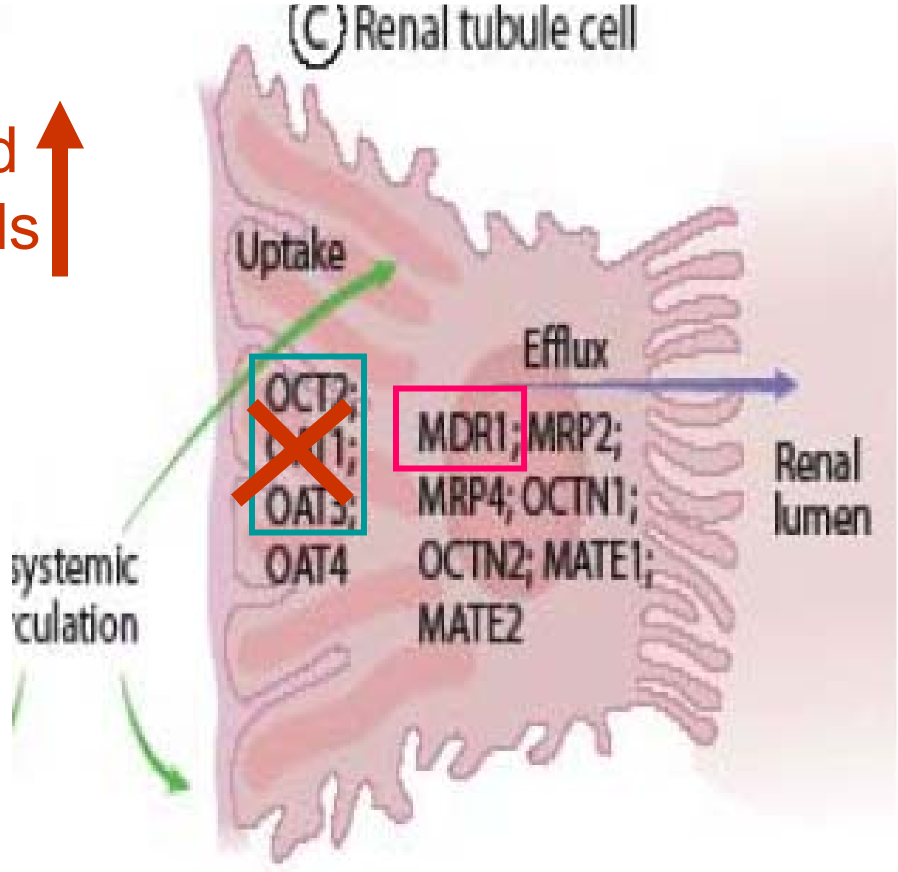
- OCT2
- OAT1
- OAT3

Efflux

(secretion to urine)

- **P-gp (MDR1)**

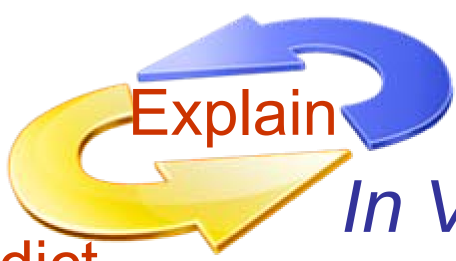
Blood Levels ↑



Inhibitor	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Probenecid	Cephradine	Cephradine Exposure ↑	3.6-fold ↑
Cimetidine	Metformin	Metformin Exposure ↑	1.4-fold ↑

Predicting Drug-Drug Interactions

- By understanding which enzymes or transporters may be involved in the ADME process and the potential for a drug to be a <u>substrate</u>, <u>inhibitor</u>, or <u>inducer</u> of that process, we can predict the potential for drug interactions.



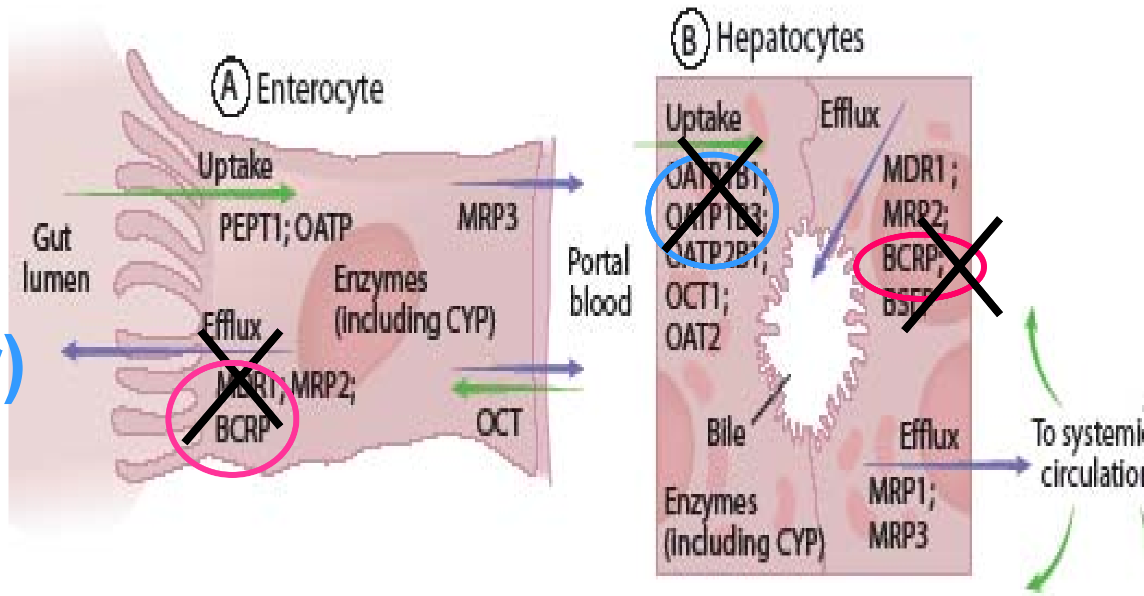
Rosuvastatin-Cyclosporine Interaction

Cyclosporine ↑ 7-fold exposure of Rosuvasatin

Possible mechanism of inhibition by cyclosporine

→OATP1B1/1B3 (uptake transporter)

→BCRP (efflux transporter)



Crestor Labeling (AstraZeneca); http://www.accessdata.fda.gov/scripts/cder/drugsatfda

Simonson SG, et al. Clin Pharmacol Ther. 2004; 76(2):167; Kesjutaki JE, et al, Clini Pharmacol Ther 2009; 86:197; Tomlinson B, Clin Pharmacol Ther 2010

OATP-, BCRP-based Interactions

- **Cyclosporine inhibits other OATP or BCRP substrates**

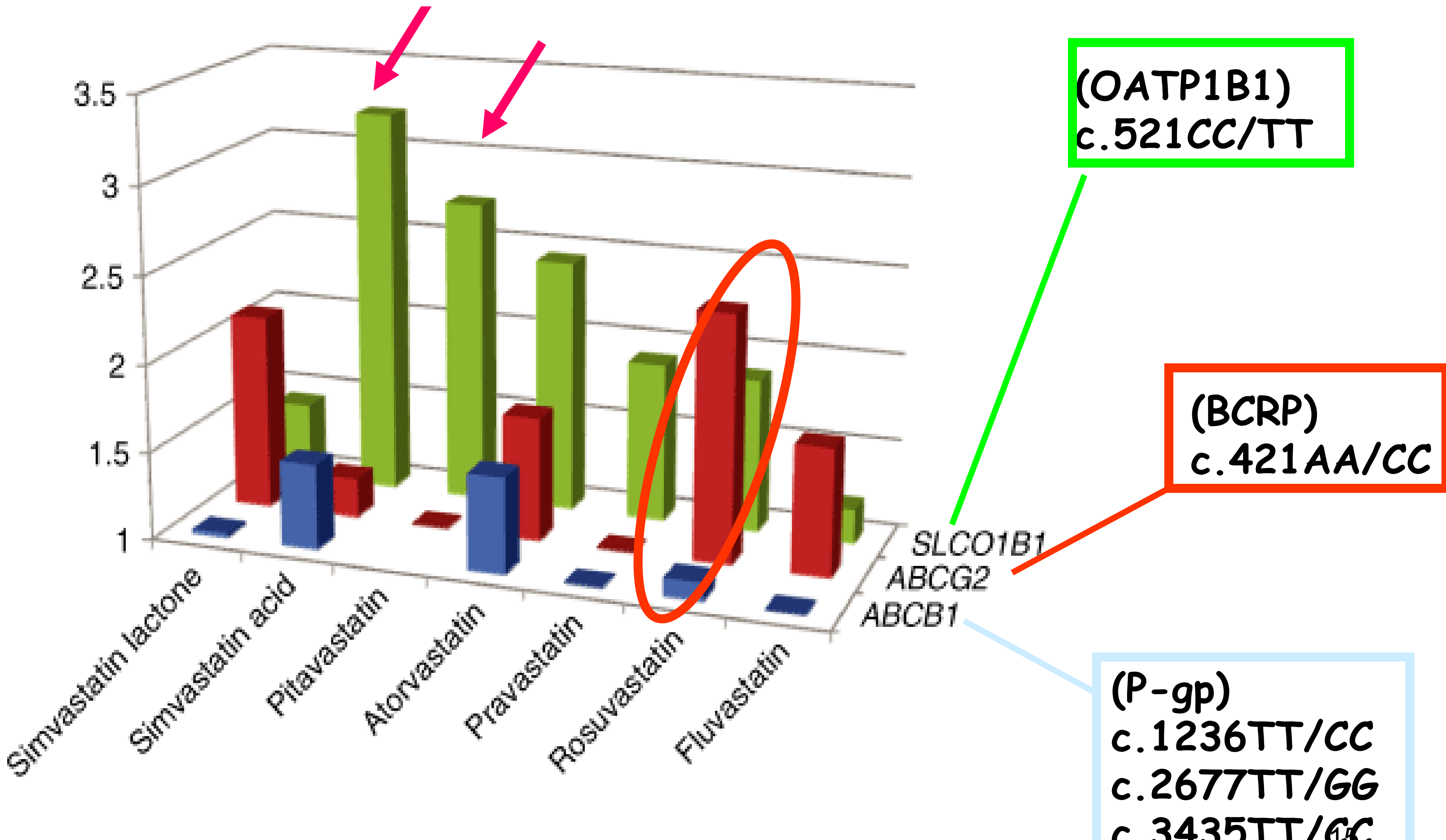
  e.g. Pitavastatin is a substrate of OATP1B1/1B3 and BCRP
  - Cyclosporine ↑ pitavastatin exposure 4.6-fold.
- **Rosuvastatin is inhibited by other OATP or BCRP inhibitors**
  - Lopinavir/ritonavir ↑ rosuvastatin exposure 2-fold
  - Lopinavir/ritonavir are inhibitors of OATP1B1/1B3 based on *in vitro* studies

Role of transporters in the disposition of a drug

- Can be determined by
  - Genetic studies (polymorphism)
    - Comparative PK in people with gene of normal function vs. reduced/absent function
  - Specific inhibitors

Fold-Change in Plasma AUC

- Effect of Transporter Genetics -



Data from Niemi M, Clin Pharmacol Ther 87:130, January 2010

Relative contribution of each transporter/enzyme on the disposition of statin drugs is different

OATP1B1, BCRP, P-gp

CYP3A4, CYP2C8, CYP2C9

Depending on inhibitor specificity for these transporters/enzymes, interaction with different statins may be different

Evaluation of NME as a Substrate for Transporters—Other Drugs' Effect on NME

All NMEs

Determine whether NME is a P-gp and/or BCRP substrate *

Refer to P-gp and BCRP decision tree for the need to conduct *in vivo* studies**

Hepatic or biliary Secretion major? e.g., ≥ 25% total clearance?

Yes

Determine whether NME is an OATP1B1 or OATP1B3 Substrate*

Refer to OATP1B1/1B3 decision tree for the need to conduct *in Vivo* studies**

Renal active secretion major? e.g., ≥ 25% total clearance?

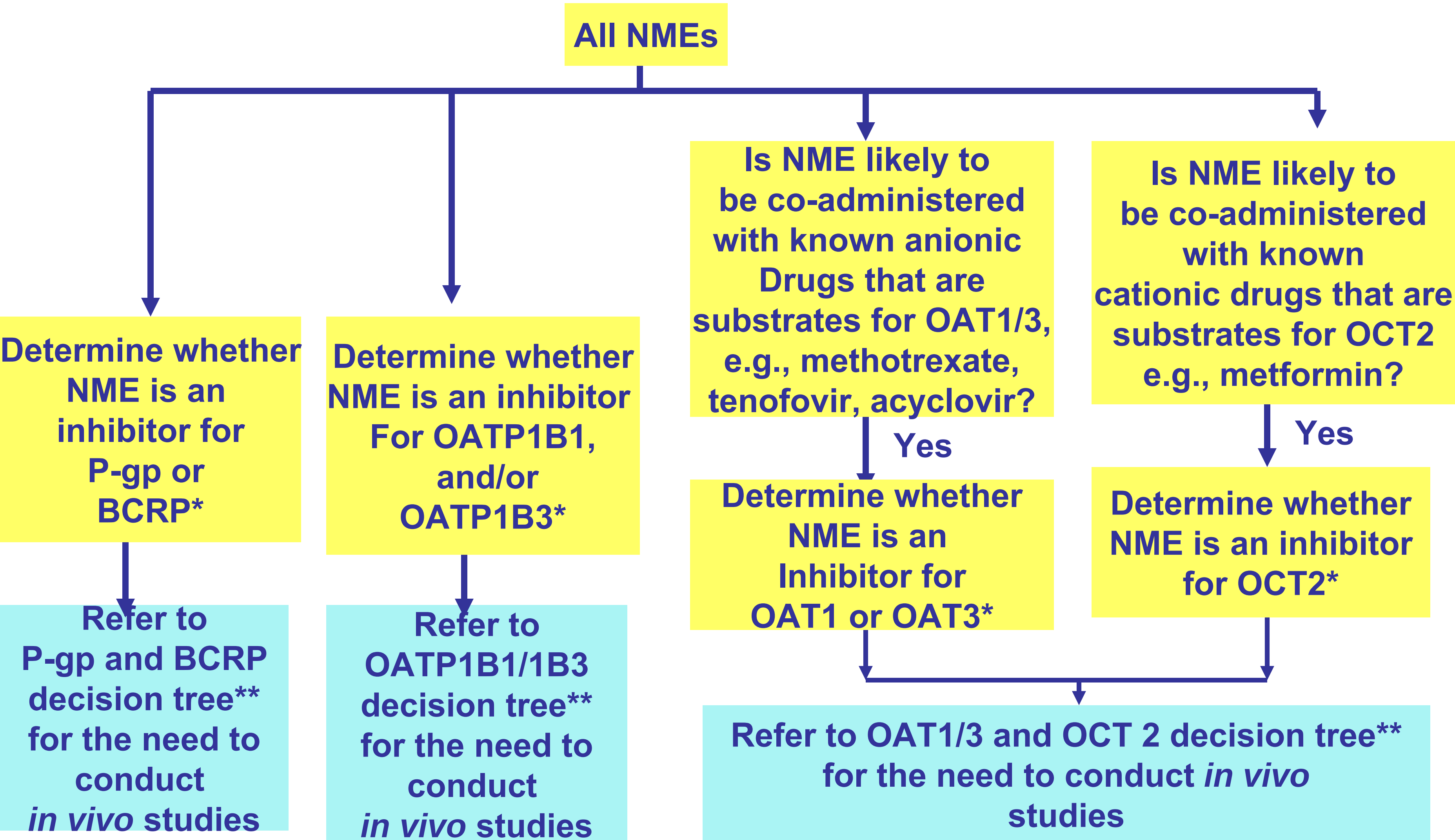
Yes

Determine whether NME is an OAT1, OAT3 or OCT2 substrate*

Refer to OAT1/3 and OCT2 decision tree for the need to conduct *in vivo* studies**

* The sponsor has the option to use *in vitro* tools first for the evaluation.
** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter

Evaluation of NME as an Inhibitor for Transporters—NMEs' Effect on Other Drugs



* The sponsor has the option to use *in vitro* tools first for the evaluation.

** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter

Examples of Transporter Substrates

Transporter	Gene	Substrates
P-gp	*ABCB1*	Aliskiren, ambrisentan, colchicine, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	*ABCG2*	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan
OATP1B1	*SCLO1B1*	Atrasentan, bosentan, ezetimibe, irinotecan, statins (e.g., atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin), repaglinide, rifampin, valsartan, olmesartan
OATP1B3	*SCLO1B3*	Statins (e.g., atorvastatin, rosuvastatin, pitavastatin), telmisartan, valsartan, olmesartan, rifampin
OCT2	*SLC22A2*	Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin
OAT1	*SLC22A6*	acyclovir, adefovir, ciprofloxacin, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine
OAT3	*SLC22A8*	Bumetanide, cimetidine, furosemide, methotrexate, zidovudine, sitagliptin, tenofovir

Please note this is not an exhaustive list and some are based on *in vitro* data. For an updated list, see the following: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Examples of Transporter Inhibitors and Inducers

Transporter	Gene	Inhibitors	Inducers
P-gp	*ABCB1*	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St John's Wort, tipranavir/ritonavir
BCRP	*ABCG2*	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known
OATP1B1	*SCLO1B1*	Cyclosporine, eltrombopag, lapatinib, lopinavir, rifampin, ritonavir,	Not known
OATP1B3	*SCLO1B3*	Cyclosporine, lopinavir, rifampin, ritonavir	Not known
OCT2	*SLC22A2*	Cimetidine, cetirizine, desipramine, quinidine	Not known
OAT1	*SLC22A6*	Probenecid, diclofenac	Not known
OAT3	*SLC22A8*	Probenecid, cimetidine	Not known

Please note this is not an exhaustive list and some are based on *in vitro* data. For an updated list, see the following: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Transporter Information in Drug Labeling

Transporter	Drug Names*
P-gp	Aliskiren, ambrisentan, [aprepitant], *clarithromycin*, colchicine, ***cyclospoprine,*** [dexvenafaxine], *dronedarone*, [eltrombopag], ***everolimus,*** fexofenadine, [fosaprepitant], [ixabepilone], ***lapatinib,*** ***maraviroc, nilotinib***, *paliperidone*, posaconazole, [prasugrel], [[propafenone]], propranolol, ***ranolazine,*** saxagliptin, silodosin, sirolimus, sitagliptin, ***tipranavir**, tolvaptan***, topotecan, [vorinostat]
OATP1B1	Atorvastatin, *cyclosporine*, *eltrombopag****, *lapatinib*, valsartan
OATP	Ambrisentan
OAT	Sitagliptin (OAT3)
OCT	Metformin, pramipexole, [saxagliptin], [sitagliptin], varenicline (OCT2)
BCRP	Lapatinib, topotecan
MRP	Mycophenolate (MRP2), [ixabepilone] (MRP1),valsartan (MRP2)

HIGHLIGHTS

*Not an extensive list: data based on a preliminary survey of electronic PDR and Drugs@FDA on September 18, 2009. They are substrates, *inhibitors*, ***both substrates and inhibitors***, [not a substrate or an inhibitor], or [[not studies as a substrate or an inhibitor]]; **:Tipranavir is also a P-gp inducer *** an inhibitor; its labeling contains a list of OATP1B1 substrates

<Huang, SM, Zhang L, Giacomini KM, Clin Pharmacol Ther, January 2010>

Labeling Example
Atorvastatin
Drug Interactions Section

- **7.3 Cyclosporine:** Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 10 mg and cyclosporine 5.2 mg/kg/day compared to that of LIPITOR alone [see *Clinical Pharmacology (12.3)*]. In cases where co-administration of LIPITOR with cyclosporine is necessary, the dose of LIPITOR should not exceed 10 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)*].

Labeling Example
Eltrombopag
Drug Interactions Section

- **7.2 Transporters**

  In vitro studies demonstrate that eltrombopag is an inhibitor of the organic anion transporting polypeptide OATP1B1 and can increase the systemic exposure of other drugs that are substrates of this transporter (e.g., benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide, repaglinide, rifampin). In a clinical study of healthy adult subjects, administration of a single dose of rosuvastatin following repeated daily PROMACTA dosing increased plasma rosuvastatin AUC0-∞ by 55% and Cmax by 103% *[see Clinical Pharmacology (12.3)]*.

  Use caution when concomitantly administering PROMACTA and drugs that are substrates of OATP1B1. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 and consider reduction of the dose of these drugs. In clinical trials with eltrombopag, a dose reduction of rosuvastatin by 50% was recommended for coadministration with eltrombopag.

Conclusion

- Understanding transporters and their interactions provides a mechanistic approach to
  - Explain variability in pharmacokinetics, pharmacodynamics, and safety in clinical trials
  - Identify patients at risk of developing adverse events associated with the drug in question or at risk drug combinations
  - Lead to actionable steps to manage the interactions

Tipping point for specific studies during development

- What are the clinical questions?
- What transporters are mature enough to be studied?
- How to evaluate NME as transporter substrates?
- How to evaluate NME as transporter inhibitors?
- Interplay with metabolizing enzymes?
- What label information would be useful to prescribers?

Questions for the Advisory Committee

.fda.gov

Evaluation of NME as a Substrate for Transporters—Other Drugs' Effect on NME

All NMEs

Hepatic or biliary Secretion major? e.g., ≥ 25% total clearance?

Renal active secretion major? e.g., ≥ 25% total clearance?

Yes

Yes

Determine whether NME is a P-gp and/or BCRP Substrate*

Determine whether NME is an OATP1B1 or OATP1B3 Substrate*

Determine whether NME is an OAT1, OAT3 or OCT2 substrate*

Refer to P-gp and BCRP decision tree for the need to conduct *in vivo* studies**

Refer to OATP1B1/1B3 decision tree for the need to conduct *in Vivo* studies**

Refer to OAT1/3 and OCT2 decision tree for the need to conduct *in vivo* studies**

* The sponsor has the option to use *in vitro* tools first for the evaluation.

** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter

Question 1

For evaluation of NMEs as potential substrates of transporters:

a. Do you agree that P-gp, BCRP, OATP1B1/1B3, OAT1/3 and OCT2 are the major transporters that should be routinely evaluated based on the proposed flow chart during drug development? ***[VOTING]***

b. What transporter(s) should be included in the flow chart for routine study and why?

c. What alternative criteria would you suggest to identify transporters that would have clinical significance and should be studied?

Evaluation of NME as an Inhibitor for Transporters—NMEs' Effect on Other Drugs

All NMEs

Determine whether NME is an inhibitor for P-gp or BCRP*

Refer to P-gp and BCRP decision tree for the need to conduct *in vivo* studies**

Determine whether NME is an inhibitor For OATP1B1, and/or OATP1B3*

Refer to OATP1B1/1B3 decision tree for the need to conduct *in vivo* studies**

Is NME likely to be co-administered with known anionic Drugs that are substrates for OAT1/3, e.g., methotrexate, tenofavir, acyclovir?

Yes

Determine whether NME is an Inhibitor for OAT1 or OAT3*

Is NME likely to be co-administered with known cationic drugs that are substrates for OCT2 e.g., metformin?

Yes

Determine whether NME is an inhibitor for OCT2*

Refer to OAT1/3 and OCT 2 decision tree for the need to conduct *in vivo* studies**

* The sponsor has the option to use *in vitro* tools first for the evaluation.

** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter

Question 2

For evaluation of NMEs as potential inhibitors of transporters:

a. Do you agree that P-gp, BCRP, OATP1B1/1B3, OAT1/3 and OCT2 are the major transporters that should be routinely evaluated based on the proposed flow chart during drug development? ***[VOTING]***

b. What transporter(s) should be included in the flow chart for routine study and why?

c. What alternative criteria would you suggest to identify transporters that would have clinical significance and should be studied?

Acknowledgements

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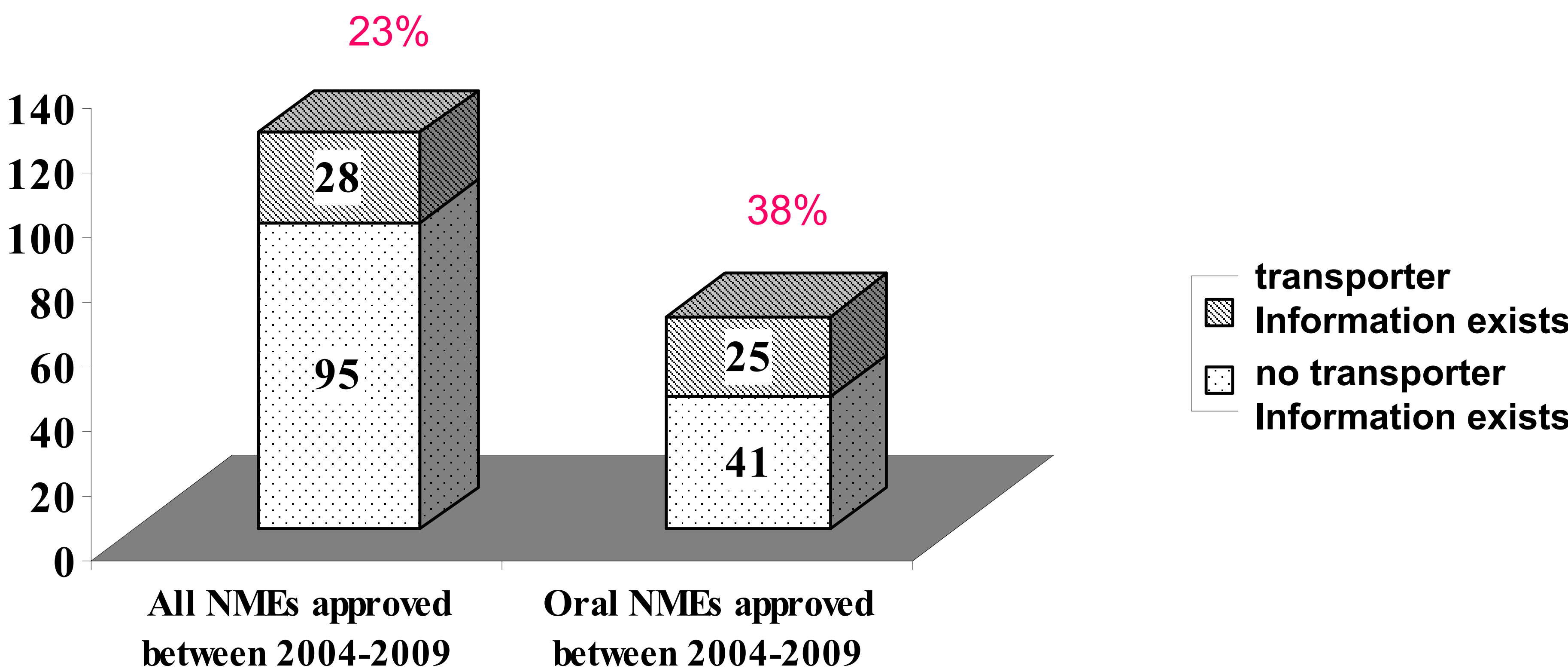
- Office of Clinical Pharmacology/OTS
- International Transporter Consortium
- Janet Woodcock/Critical Path Initiative

References

- **Transporter Whitepaper**
  - Giacomini K, Huang S-M, Tweedie, D, et al, Nature Reviews Drug Discovery 2010, 9, 215-236.
- **Commentary**
  - Huang and Woodcock, Nature Reviews Drug Discovery 2010, 9, 175-176
- **International Transporter Consortium**
  - S-M Huang, L Zhang, K Giacomini. The International Transporter Consortium (ITC): A collaborative group of scientists from academia, industry and FDA. Clin Pharm Ther. 87(1):32-36, (2010)
- **Drug Development and Drug Interactions**
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
- **Draft Drug Interaction Guidance**
  - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

Transporter information in labeling



Unpublished data

Learned from CYP experience

- There exist many drug interactions
  - Understanding the CYPs and transporters provides a starting point
- *In vitro* models are useful to predict drug interaction potential